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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,762	11/14/2001	J. Keith Joung	MTV-030.02	2226

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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,762	JOUNG ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-9 are pending. Withdrawn claims 10-20 were cancelled by amendment, filed 10/18/2004.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/18/2004 has been entered.

Priority

3. The instant application is a continuation in part of 09/858,852, filed 5/16/2001, which claims benefit of Provisional application no. 60/204,509, filed 5/16/2000.

Specification

4. The disclosure is objected to because of the following informalities: In the Brief Description of the Figures, reference should be made to each individual drawing, *i.e.*, --1A, 1B, 1C--, instead of merely "Fig. 1", and so forth.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim Rejections - 35 USC § 112, Second Paragraph

Withdrawn Rejections

5. The rejections of claims 1-9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, and as being incomplete for omitting essential steps, are withdrawn in view of applicant's amendments to the claims, filed 10/18/2004.

New Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the language "a transcriptional regulatory sequence comprising one binding site for the DNA binding domain of (a)", which renders the claim vague and indefinite, because it is unclear what "(a)" is, and because step (a) of claim 1 appears to refer to a chimeric *gene*, whereas "the DNA binding domain" appears to be a component of a fusion *protein*.

Withdrawn Claim Rejections - 35 USC § 112, First Paragraph

7. The rejections of claims 1-9 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of applicant's arguments, filed 10/18/2004.

Applicant argues that the genus of reporter genes is described throughout the specification and that the structures and functions of these reporter genes were entirely conventional and known at the time of filing.

8. The rejection of claims 1-9 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and / or use the invention commensurate in scope with these claims, is withdrawn in view of applicant's arguments, filed 10/18/2004.

Applicant argues that the specification as filed clearly sets forth how to practice the claimed methods using any reporter gene and that the practitioner could readily select any reporter gene from the lists recited or known in the art in which the practitioner is presumably already interested, according to the disclosure, and could readily test whether or not dimerization could be evaluated, again according to the disclosure. Applicant argues that the specification fully enables the methods as claimed, regardless of the reporter gene selected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 3-5 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Menzel et al., Pub. No. US 2003/0003449 (priority to Jul. 23, 1998).

The claims are drawn to a method for selecting a dimerizing test polypeptide, comprising: providing a population of host cells wherein each host cell contains (a) a chimeric gene which encodes a fusion protein, including one or more DNA-binding domains, an activation domain, and a test polypeptide, (b) a reporter gene operably linked to a transcriptional regulatory sequence which includes two or more binding sites (DBD recognition elements) for the DNA-binding domain of step (a), wherein binding of a single copy of the fusion protein to the transcriptional regulatory sequence of the reporter gene does not result in a desired level of expression of the reporter gene; wherein dimerization of two copies of the fusion protein to each other and binding of the dimerized fusion protein to the transcriptional regulatory sequence of the reporter gene results in a desired level of expression of the reporter gene; and isolating host cells exhibiting a desired level of expression of the reporter gene, thereby selecting a dimerizing test polypeptide.

Menzel et al., throughout the publication and especially at para [0131] – [0137], [0252] – [0257], Figures 1 and 5, teach a method for selecting a dimerizing test polypeptide, comprising: providing a population of host cells that are *E. coli* SAD4 host strain cells, wherein each host cell contains (a) a chimeric gene *E. coli AraC* gene, that encodes a fusion protein, including a DNA binding domain, which is intimately associated with a transcriptional activation function (that reads on an activation domain), and a test polypeptide that is a yeast leucine zipper dimerization domain, (b) a reporter gene that is a mutant GCN4, operably linked to an *araBAD* operon transcriptional regulatory sequence, which includes two binding sites (DBD recognition elements) that are the $araI_1$ and $araI_2$ half-sites of the operon for the DNA-binding domain of step (a), wherein lack of dimerization does not support activation of the reporter gene, thereby demonstrating that binding of a single copy of the fusion protein to the transcriptional regulatory sequence of the reporter gene does not result in a desired level of expression of the reporter gene; and wherein dimerization of two copies of the fusion protein to each other and binding of the dimerized fusion protein to the transcriptional regulatory sequence of the reporter gene results in a desired level of expression of the reporter gene. Menzel et al. further teach selecting a dimerizing test polypeptide from cDNA sequences of, *e.g.*, new genes of interest, either complete or partial, fused to the DNA binding/activation domain of araC; where the dimerization capacity of the so generated chimeras may be tested by measuring their ability to activate transcription of an *AraC*-dependent promoter, and isolating host cells exhibiting a desired level of expression of the reporter gene, thereby selecting a dimerizing test polypeptide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 2 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Menzel et al.**, Pub. No. US 2003/0003449 (priority to Provisional application 60/093,855, filed Jul. 23, 1998) and **Golemis et al.**, US 6,326,150.

The claims are drawn to a method for selecting a dimerizing test polypeptide, comprising: providing a population of host cells wherein each host cell contains (a) a chimeric gene which encodes a fusion protein, including one or more DNA-binding domains, an activation domain, and a test polypeptide, (b) a reporter gene operably linked to a transcriptional regulatory sequence which includes two or more binding sites (DBD recognition elements) for the DNA-binding domain of step (a), wherein binding of a single copy of the fusion protein to the transcriptional regulatory sequence of the reporter gene does not result in a desired level of expression of the reporter gene; wherein dimerization of two copies of the fusion protein to each other and binding of the

dimerized fusion protein to the transcriptional regulatory sequence of the reporter gene results in a desired level of expression of the reporter gene; and isolating host cells exhibiting a desired level of expression of the reporter gene, thereby selecting a dimerizing test polypeptide; wherein the host cell further comprises a second reporter gene operably linked to a transcriptional regulatory sequence comprising one binding site for the DNA binding domain of the fusion protein, and wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell.

Menzel et al., throughout the publication and especially at para [0131] – [0137], [0252] – [0257], Figures 1 and 5, teach a method for selecting a dimerizing test polypeptide, comprising: providing a population of host cells that are *E. coli* SAD4 host strain cells, wherein each host cell contains (a) a chimeric gene *E. coli AraC* gene, that encodes a fusion protein, including a DNA binding domain, which is intimately associated with a transcriptional activation function (that reads on an activation domain), and a test polypeptide that is a yeast leucine zipper dimerization domain, (b) a reporter gene that is a mutant GCN4, operably linked to an *araBAD* operon transcriptional regulatory sequence, which includes two binding sites (DBD recognition elements) that are the $araI_1$ and $araI_2$ half-sites of the operon for the DNA-binding domain of step (a), wherein lack of dimerization does not support activation of the reporter gene, thereby demonstrating that binding of a single copy of the fusion protein to the transcriptional regulatory sequence of the reporter gene does not result in a desired level of expression of the reporter gene; and wherein dimerization of two copies of the fusion protein to each other and binding of the dimerized fusion protein to the transcriptional regulatory

sequence of the reporter gene results in a desired level of expression of the reporter gene. Menzel et al. further teach selecting a dimerizing test polypeptide from cDNA sequences of, *e.g.*, new genes of interest, either complete or partial, fused to the DNA binding/activation domain of araC; where the dimerization capacity of the so generated chimeras may be tested by measuring their ability to activate transcription of an *AraC*-dependent promoter, and isolating host cells exhibiting a desired level of expression of the reporter gene, thereby selecting a dimerizing test polypeptide.

Menzel et al. does not teach methods for selecting a dimerizing test polypeptide, comprising: providing a population of host cells wherein the host cell further comprises a first and a second reporter gene operably linked to a transcriptional regulatory sequence comprising one binding site for the DNA binding domain of the fusion protein, and wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell.

Golemis et al., US 6,326,150, throughout the patent, and especially at col. 1, lines 30-58 and Figure 1A, teach a basic interaction trap assay system comprising a first reporter gene that is LEU2 operably linked to a first protein binding site that is LexA and a second reporter gene, which is LacZ, and that is also operably linked to LexA.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used methods for selecting a dimerizing test polypeptide, comprising: providing a population of host cells wherein each host cell contains a chimeric gene which encodes a fusion protein, and a reporter gene operably linked to a transcriptional regulatory sequence; wherein the host cell further comprises a

first and a second reporter gene operably linked to a transcriptional regulatory sequence comprising one binding site for the DNA binding domain of the fusion protein, and wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell.

One of ordinary skill in the art would have been motivated to use methods comprising host cells that comprise a second reporter gene operably linked to a transcriptional regulatory sequence comprising one binding site for the DNA binding domain of the fusion protein, because these two reporters allow selection for transcriptional activation by permitting selection for viability when cells are plated on medium lacking a required amino acid and discrimination based on color when the cells are grown on medium containing X-gal, as taught by Golemis et al. One of ordinary skill in the art would have been motivated to use methods wherein the desired level of expression of the reporter gene confers a growth advantage on the host cell, in order to select cells that comprise the sought for dimerizing test polypeptides, as taught by Golemis et al.

One of ordinary skill in the art would have had a reasonable expectation of success in using methods for selecting dimerizing test polypeptides comprising a first and a second reporter gene and selection systems where expression of the reporter gene confers a growth advantage on the host cell, because two reporter gene selection systems were used in basic interaction trap assays known in the art and because auxotroph selection systems were also well known in the art.

11. Claims 1, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Menzel et al.**, Pub. No. US 2003/0003449 (priority to Provisional application 60/093,855, filed Jul. 23, 1998) and **Jappelli et al.**, Biochem. Biophys. Res. Commun. (1999) Vol. 266, pp. 243-247.

The claims are drawn to a method for selecting a dimerizing test polypeptide, comprising: providing a population of host cells wherein each host cell contains (a) a chimeric gene which encodes a fusion protein, including one or more DNA-binding domains, an activation domain, and a test polypeptide, (b) a reporter gene operably linked to a transcriptional regulatory sequence which includes two or more binding sites (DBD recognition elements) for the DNA-binding domain of step (a), wherein binding of a single copy of the fusion protein to the transcriptional regulatory sequence of the reporter gene does not result in a desired level of expression of the reporter gene; wherein dimerization of two copies of the fusion protein to each other and binding of the dimerized fusion protein to the transcriptional regulatory sequence of the reporter gene results in a desired level of expression of the reporter gene; and isolating host cells exhibiting a desired level of expression of the reporter gene thereby selecting a dimerizing test polypeptide; wherein the chimeric gene is a member of a library comprising a plurality of sequences encoding random test polypeptides, and wherein the library comprises at least 10^7 members.

Menzel et al., throughout the publication and especially at para [0131] – [0137], [0252] – [0257], Figures 1 and 5, teach a method for selecting a dimerizing test polypeptide, comprising: providing a population of host cells that are *E. coli* SAD4 host

strain cells, wherein each host cell contains (a) a chimeric gene *E. coli AraC* gene, that encodes a fusion protein, including a DNA binding domain, which is intimately associated with a transcriptional activation function (that reads on an activation domain), and a test polypeptide that is a yeast leucine zipper dimerization domain, (b) a reporter gene that is a mutant GCN4, operably linked to an *araBAD* operon transcriptional regulatory sequence, which includes two binding sites (DBD recognition elements) that are the $ara I_1$ and $ara I_2$ half-sites of the operon for the DNA-binding domain of step (a), wherein lack of dimerization does not support activation of the reporter gene, thereby demonstrating that binding of a single copy of the fusion protein to the transcriptional regulatory sequence of the reporter gene does not result in a desired level of expression of the reporter gene; and wherein dimerization of two copies of the fusion protein to each other and binding of the dimerized fusion protein to the transcriptional regulatory sequence of the reporter gene results in a desired level of expression of the reporter gene. Menzel et al. further teach selecting a dimerizing test polypeptide from cDNA sequences of, *e.g.*, new genes of interest, either complete or partial, fused to the DNA binding/activation domain of araC; where the dimerization capacity of the so generated chimeras may be tested by measuring their ability to activate transcription of an *AraC*-dependent promoter, and isolating host cells exhibiting a desired level of expression of the reporter gene, thereby selecting a dimerizing test polypeptide.

Menzel et al. does not teach methods for selecting a dimerizing test polypeptide, comprising: providing a population of host cells wherein each host cell contains a chimeric gene which encodes a fusion protein, and a reporter gene operably linked to a

transcriptional regulatory sequence; wherein the chimeric gene is a member of a library comprising a plurality of sequences encoding random test polypeptides, and wherein the library comprises at least 10^7 members.

Jappelli et al., Biochem. Biophys. Res. Commun. (1999) Vol. 266, pp. 243-247, throughout the publication, and especially at the abstract, p. 243, para 5-p. 247, para 1, Tables 1 and 2, teach methods of identifying dimerizing polypeptides using a homodimerization system in *E. coli*, where fusion proteins libraries comprising a plurality of sequences encoding random test polypeptides were selected for the capacity to dimerize in a bacteriophage λ repressor dimerization assay, and wherein the library comprises at least 10^7 members, as evidenced by highest lysing phage dilutions of 10^{-7} that produced a visible lysis of the bacterial lawn.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to have used methods for selecting a dimerizing test polypeptide, comprising: providing a population of host cells wherein each host cell contains a chimeric gene which encodes a fusion protein, and wherein the chimeric gene is a member of a library comprising a plurality of sequences encoding random test polypeptides, and wherein the library comprises at least 10^7 members.

One of ordinary skill in the art would have been motivated to use methods wherein the chimeric gene is a member of a library comprising a plurality of sequences encoding random test polypeptides, and wherein the library comprises at least 10^7 members in order to identify dimerizing test polypeptides, because Jappelli et al. at p. 247, para 1, state: "Regardless of the specific mechanism of interaction, the

identification of novel sequences promoting protein oligomerization may be important to understand the evolution of natural protein structures. In addition, it may be interesting for protein engineering applications."

One of ordinary skill in the art would have had a reasonable expectation of success in using methods for selecting dimerizing test polypeptides, wherein the chimeric gene is a member of a library comprising a plurality of sequences encoding random test polypeptides, and wherein the library comprises at least 10^7 members, because Jappelli et al. used such libraries to identify dimerizing polypeptides in homodimerization bacterial systems.

Conclusion

12. Claims 1-9 are rejected.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

ms

PADMASHRI PONNALURI
PRIMARY EXAMINER